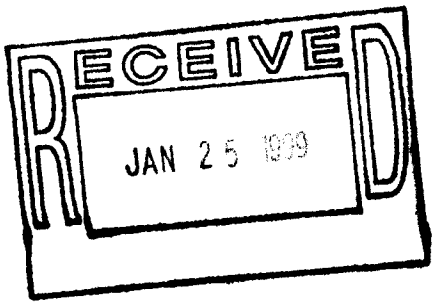
Myron A. Mehlman, Ph.D.
7 Bouvant Drive • Princeton, NJ 08540
Tel.: 609-683-1493 • Fax: 609-683-0838
E-mail: psp@erols.com

January 21, 1999

Dr. Kenneth Olden
Director, NIEHS
P.O. Box 12233
Research Triangle Park, NC 27709



Dear Dr. Olden,

At a meeting on December 2–3, 1998, the NTP Board of Scientific Counselors voted 6 to 5 not to list MTBE as being "Reasonably Anticipated to be a Human Carcinogen" despite very strong and sufficient evidence that MTBE is a carcinogen in laboratory animals.

Some of the Board members who voted against listing MTBE, as well as industry representatives who made presentations at the Board meeting, stated that MTBE is clearly an animal carcinogen. What is disconcerting is that some members of the Board did not vote according to the criteria established by NTP for listing agents in the *Report on Carcinogenesis.*

The criteria specify that an agent be listed in the report as "Reasonably Anticipated to be a Human Carcinogen" if:

> **"there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and / or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites; (2) by multiple routes of exposure or (3) to an unusual degree with regard to incidence, site or type of tumor, or age of onset."**

The criteria also allow consideration of other relevant information in making conclusions regarding the carcinogenicity of an agent in humans or experimental animals. "For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but for which there are *compelling data* indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans." Board members who voted against listing MTBE noted that there was no compelling mechanistic data on MTBE showing that it acts through mechanisms which do not operate in humans. The Board acknowledged that the mechanisms of MTBE-induced carcinogenicity are unknown.

Review of Available Cancer Bioassay Studies

There is general agreement among experts in chemical carcinogenesis that a substance that causes cancer in significant numbers of experimental animals in well-conducted assays poses a presumptive carcinogenic risk to humans, even in the absence of confirmatory epidemiological data. This principle is accepted by scientific and medical experts throughout the world and has served for many years as the basis for sound public health policy and regulatory action on carcinogens. For example, the International Agency for Research on Cancer (IARC) of the World Health Organization, in its Supplement 7 of the Monograph (1987), states:

> Information compiled from the first 41 volumes of IARC monographs shows that, of the 44 agents for which there is sufficient or limited evidence of carcinogenicity to humans, all 37 that have been tested adequately experimentally produce cancer in at least one animal species ... Thus, in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

In the world's largest animal study sponsored by the U.S. EPA and the U.S. FDA (Staffa, J.A. and Mehlman, M.A.), "Innovation in Cancer Risk Assessment [ED_{01} Study]", concerning a single carcinogenic chemical in an effort to determine the answer to the question of relevance of using extrapolation from high doses to low doses, it was found by U.S. Government scientists, as officials of federal regulatory policy, that:

> There should be no debate over a key principle that has shaped both our investigations and the regulatory posture of FDA and EPA, namely that no level of exposure to a toxic substance greater than zero can be assumed to be without potentially harmful effects ... The evidence from the ED_{01} study ... has provided a massive and overwhelming experimental profile and the data base lends support to regulatory policies.

Scientific evidence from three separate animal bioassay studies (two different species of rats and in mice) demonstrates that chronic exposure to MTBE by either oral or inhalation routes of exposure cause cancers in animals.

Inhalation exposure to MTBE causes increased incidence of renal and testicular tumors in male rats and liver tumors in mice. Oral administration of MTBE produced a statistically significant increased incidence of lymphomas and leukemias in female rats and testicular tumors in male rats.

Thus, the weight of evidence demonstrates that MTBE is a probable human carcinogen. This means that some humans exposed to MTBE will be at risk of developing cancer.

Carcinogenicity Bioassay by Inhalation in F344 Rats

Chung et al. reported increased incidences of uncommon renal tumors in male rats exposed to MTBE compared with controls. Three of the eight renal tumors in the 3000 ppm group were carcinomas. In addition, two males rats in the low exposure group (400 ppm) had preneoplastic adenomatous hyperplasia in renal tubules. In female rats, there was one renal tubular adenoma in the middle-exposure group. This bioassay was significantly shortened for the high-dose group thereby decreasing the total number of animals at risk for developing tumors. An exposure related increase in testicular tumors was also observed in male rats.

Carcinogenicity Bioassay by Inhalation in CD-1 Mice

Burleigh-Flayer et al. reported an increased incidence of hepatocellular carcinomas in male mice exposed to the highest dose of MTBE, and an increased incidence of liver tumors (adenomas and carcinomas combined) in female mice exposed to the highest dose. The duration of bioassay was 18 months instead of the usual 24 month period routinely used in cancer bioassays. Therefore, it is likely that additional tumors would have been detected had this study been continued for the usual 24 month exposure period.

Carcinogenicity Bioassay by Gavage in Sprague-Dawley Rats

Belpoggi, Soffritti, and Maltoni reported that MTBE causes a significant dose related increase in interstitial cell adenomas (Leydig cell tumors) in male rats and significant increases in haemolymphoreticular neoplasia of lymphocytic origin (lymphoblastic lymphomas, lymphoblastic leukemias and lymphoimmunoblastic lymphomas) in female rats. In addition, haemolymphoreticular dysplasias were increased in exposed female rats.

In summary, carcinogenicity studies on MTBE have shown that this chemical induces benign and malignant tumors at multiple sites, in multiple species, by multiple routes of exposure. In addition, metabolites of MTBE (formaldehyde and t-butyl alcohol) are carcinogenic in animals and there is strong evidence on the carcinogenicity of formaldehyde in people.

Historically, for tran-species cancer-causing chemicals, as more information becomes available, the permissible exposure levels have been drastically reduced. For example, the permissible exposure level for benzene was reduced from 100 ppm to 1 ppm. It is now recommended that the permissible exposure level be reduced to 0.1 ppm. For vinyl chloride, the permissible exposure level was also reduced from 100 ppm to 1 ppm. Recently, the permissible exposure level for 1,3-butadiene was reduced from 1,000 ppm to 1 ppm, with a level of 0.2 ppm recommended.

Pregnant women, young children, people with asthma, people on medications, sensitive individuals, and the elderly are at an even greater risk of developing life-

threatening cancers when they are exposed to MTBE vapors, contaminated water, or automobile exhaust containing this chemical. As you know, North Carolina was allowed to discontinue the use of oxygenated fuels because MTBE in gasoline *did not* significantly reduce ambient CO levels and MTBE in gasoline posed increased cancer risk to the citizens of North Carolina.

Conclusion

Hence, good public health policy dictates another review of MTBE by the Board with proper consideration of the criteria that have been established for listing agents in the *Report on Carcinogens*. It is clear that the Board was influenced by presentations at the meeting and claims that tumors induced by MTBE may not be applicable to humans because of various hypothetical mechanisms. However, no compelling data supporting those claims has emerged. The millions of U.S. citizens who are exposed to this chemical every day in the air they breathe or the water they drink deserve an unbiased evaluation of carcinogenic agents that are being released into our environment.

Yours truly,

Myron A. Mehlman, Ph.D.

Adjunct Professor, Mt. Sinai School of Medicine
Adjunct faculty member, New York University School of Medicine
Adjunct Professor, UMDNJ — Robert Wood Johnson Medical School
Former President, American College of Toxicology
Former President, International Society of Exposure Analysis
Former Director of Toxicology, Mobil Oil Corporation

cc: George Lucier
William Jameson

MAM/ac